

Alcohol consumption and risk of colorectal cancer in a cohort of Finnish men

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We investigated the association between self-reported alcohol ingestion and colorectal cancer in a cohort of male smokers in Finland. Among 27,109 men aged 50 to 69 years, 87 colon and 53 rectal cases were diagnosed during the five to eight years of follow-up. Among drinkers, colorectal cancer risk increased with the amount of alcohol consumed (P trend = 0.01) with risk increasing by 17 percent for each drink consumed. Both beer and spirits contributed to this increased risk. Further analyses revealed that the positive association with alcohol was primarily for colon cancer (P trend = 0.01). Interestingly, risk of colorectal cancer associated with drinking (*cf* self-reported abstinence) changed with follow-up time, suggesting an inverse association for alcohol early in follow-up, and a positive association after about three-and-a-half years of follow-up. Follow-up time did not modify the positive association with amount of alcohol among drinkers, however. Results also indicated that β -carotene supplementation may attenuate the effect of alcohol on colorectal cancer risk among drinkers. In conclusion, this study supports a role for alcohol in colon carcinogenesis and suggests that similar studies should evaluate carefully the effects of lifetime drinking habits and recent abstinence. *Cancer Causes and Control* 1996, 7, 214–223

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Introduction

Colorectal cancer is a major cause of cancer death in North America and Europe.¹ The age-adjusted incidence rates in Finland between 1988 and 1992 were 13.0/100,000 for colon cancer and 10.5/100,000 for rectal cancer in males compared with, respectively, 11.8/100,000 and 6.5/100,000 in females.² In Finland, colorectal cancer has been the third most common cancer in males, after lung and prostate cancers, since the early 1980s.²

Many studies have characterized risk factors for colorectal cancer. Large international variation in rates as well as migrant studies suggest that the environment is a

major contributor to the development of colorectal cancer.³ Some of the possible risk factors include dietary fat, and total energy and meat intake.^{4,5} Factors that might be protective include vegetables, fruits, fiber, calcium, and aspirin.^{4,8} Several studies also have evaluated the role of alcohol in colorectal cancer. Animal experiments provide no clear pattern with respect to risk with only four of eight studies showing an increase in chemically induced colorectal tumors in response to ethanol intake.⁹ Further, findings from epidemiologic studies of alcohol and colorectal cancer have not been consistent. Kune and collea-

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gues⁹ reviewed all relevant major studies conducted between 1957 and 1991. Ten of the 14 cohort studies reviewed showed a positive association between colorectal cancer and alcohol intake, seven being statistically significant. Beer was the only alcoholic beverage associated with an elevated risk, and rectal cancer was more likely than colon cancer to be associated with alcohol intake.⁹ About half of the 31 case-control studies reviewed showed a positive association between alcohol and colorectal cancer.⁹ Studies using community controls were more likely to observe associations, and in these, rectal cancer was more likely to be associated significantly with alcohol intake than colon cancer. Beer was also more likely to be associated significantly with an increased cancer risk than wine or spirits. Longnecker *et al*¹⁰ conducted a meta-analysis of 27 studies and found a weak overall alcohol/colorectal-cancer association when comparing individuals who drink 24 grams/day with nondrinkers (relative risk [RR] = 1.10, 95 percent confidence interval [CI] = 1.05-1.14).

Thus, while some studies suggest an association between beer consumption and rectal cancer, the overall role of alcohol in colorectal carcinogenesis is still not well understood. We investigated this issue by assessing the risk of colorectal cancer associated with alcohol consumption (total and specific beverages) in a cohort of male smokers in Finland.

Materials and methods

The sample population

The sample population consisted of individuals participating in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC Study) conducted in Finland. The ATBC Study was a randomized placebo-controlled clinical trial designed to evaluate the effect of α -tocopherol (50 mg/day) and β -carotene (20 mg/day) on the incidence and mortality related to lung and other cancers. The cohort consisted of 29,133 White male subjects, aged 50 to 69 years, who smoked five or more cigarettes per day and lived in southwestern Finland. Exclusion criteria included: the presence of a previous carcinoma (except non-melanoma skin cancer and *in situ* carcinoma); severe angina with exertion; chronic renal insufficiency; alcoholism; cirrhosis; supplementation with β -carotene, vitamin A, or vitamin E in excess of defined amounts; and anticoagulant use. The subjects were recruited between 1985 and 1988 and followed for five to eight years. Further details on the design and results of the ATBC Study have been published.^{11,12} This clinical trial was approved by the institutional review boards of the United States National Cancer Institute and the National Public Health Institute of Finland.

Assessment of exposure

The total amount of alcohol ingested and the type of alcoholic beverage consumed (beer, wine, spirits) were measured using a food-use questionnaire given to all participants prior to randomization. Using a color picture booklet, participants were asked to report their usual frequency of consumption over the previous 12 months and portion sizes for over 270 common food items, including specific alcoholic beverages. Complete dietary information on alcohol intake was available for 27,109 participants (93 percent) and these subjects are the basis for this study. This dietary instrument already had been evaluated for reproducibility and validity.¹³ For reproducibility, Pearson correlation coefficients varied from 0.54 (vitamin A) to 0.9 (alcohol), while for validity, Pearson correlation coefficients ranged from 0.4 (selenium) to 0.8 (alcohol).¹³ The food composition database of the National Public Health Institute in Finland was used to derive total energy and specific nutrients from the dietary questionnaire information. Total alcohol intake was calculated in grams of ethanol per day and comprised all alcoholic beverages drunk in Finland including spirits, beer, wine, fortified wine, liqueur, and miscellaneous drinks such as a gin and grapefruit mixed drink. Grams of ethanol per day from spirits, wine, and beer were each calculated separately. Drinkers were defined as those individuals who reported consumption of any alcohol while nondrinkers were subjects who reported no alcohol intake.

Assessment of other variables of interest

Variables that could have an association (positive or negative) with colorectal cancer or could be associated with alcohol intake were evaluated as possible confounders. Education, exercise, degree of urbanization, number of total cigarettes smoked, and body mass index (BMI) (wt/ht^2) were available from the baseline questionnaire and interview. Intake of meats, vegetables, fruits, coffee, total energy, fat, carbohydrate, fiber, protein, starch, sweets and sugar, fatty acids, total carotenes, β -carotene, vitamin A, vitamin E, vitamin C, vitamin D, folate, and calcium were assessed using the food-use questionnaire data. Serum total cholesterol was determined at baseline.¹¹ Trial treatment group assignment was also available.

Case identification

Incident cancers were identified through the Finnish Cancer Registry. Since 1961, hospitals, laboratories, and doctors in Finland have had to report all cancer cases to the Registry; as a result, the case ascertainment is highly accurate.¹⁴ Cancer deaths were identified through the Statistics Finland. All relevant records of colorectal

cancer cases were reviewed independently and the final cancer diagnosis assigned by two medical oncologists. In the few cases where their diagnoses disagreed, a third medical oncologist reviewed the case for final diagnosis. Cases were defined as incident cases of colon cancer (ICD-9¹⁵ code 153) and rectal cancer (code 154) diagnosed between April 1985 and August 1993. Carcinoid tumors, adenocarcinoma *in situ* and squamous cell cancers were not considered cases (10 individuals). For the five cases that had multiple colorectal cancers with different histologies, histology and diagnosis date corresponding to the earliest cancer was used and secondary cancers were excluded. Of 140 remaining cases, 87 cases were colon cancers and 53 were rectal cancers. Histologically, 138 were adenocarcinomas, one was an anaplastic carcinoma, and one was unclassified.

Statistical analyses

Cox regression methods were used to estimate the effect of alcohol consumption on the occurrence of colorectal cancer.¹⁶ These methods assume that the relative incidence rate of persons with predictors $x = x_1$ *cf* persons with predictors x_2 is constant over time, a characteristic termed the proportional hazards (PH) assumption. For computational simplification, our primary analysis used follow-up time as the underlying time metric along with age at randomization as a predictor variable (four age groups: 50-54, 55-59, 60-64, and 65-69). We confirmed our final results with the preferred, but more computer intensive, analysis using age as the underlying time metric. The effect of alcohol (total or beverage specific) was measured by using a combination of two predictors: (i) a single categorical indicator variable taking the value 0 for nondrinkers and 1 for drinkers; and (ii) either a set of three 0-1 indicator variables defined by quartiles of ethanol consumption among drinkers, a single trend variable constructed by giving incremental values of 0, 1, 2, and 3,

respectively, to each quartile, or ethanol amount as a continuous variable. Multivariable models were developed first using all the colorectal cases and then applied to the colon and rectal cases separately. Variables that produced a significant change in log-likelihoods ($P < 0.05$) or produced a > 10 percent change in the alcohol regression coefficients were kept in the model. Potential interactions between alcohol and other study factors were tested by including that factor and its interaction term in the model. Each continuous variable was categorized into quartiles derived from its distribution over the entire cohort. We examined the validity of the PH assumption by comparing the likelihoods of Cox models assuming proportionality of hazards with Cox models which relaxed the PH assumption by allowing one or more regression coefficients to be functions of time. All statistical analyses were conducted using SAS software.^{17,18}

Results

The cohort consisted of 27,109 men, aged 50 to 69 years at study entry, who smoked an average of one pack of cigarettes daily. The majority had completed only an elementary school education and 60 percent lived in small towns or rural areas. Walking was the major form of leisure exercise, while 44 percent of workers engaged in moderate to heavy physical activity on the job. While drinkers were younger and less likely to engage in moderate to heavy job-related physical activity than nondrinkers, drinkers and nondrinkers did not differ appreciably in their amount of leisure activity, place of residence, intervention group, and level of education.

Median consumption for alcohol, beer, wine, and spirits among consumers is presented in Table 1. Alcohol consumption ranged from 0 to 278 g of ethanol per day, with 89 percent of the cohort and 85 percent of the cases

Table 1. Medians and interquartile ranges^a (IR) for alcoholic beverages in ethanol (g/day) among consumers by case status, Finnish men

Beverage type		Cohort (n = 27,109)	Colorectal cases (n = 140)	Colon cases (n = 87)	Rectal cases (n = 53)
Alcohol ^b	Percent consuming alcohol	89%	85%	87%	81%
	Median (IR)	13.4 (5.3-27.7)	15.6 (6.1-34.4)	17.1 (7.5-35.5)	15.1 (4.7-24.9)
Beer	Percent consuming beer	71%	68%	74%	58%
	Median (IR)	4.6 (1.7-11.6)	5.9 (1.7-12.7)	7.4 (1.8-14.0)	5.2 (1.6-10.9)
Wine	Percent consuming wine	21%	27%	31%	21%
	Median (IR)	2.1 (0.7-4.6)	1.8 (0.7-4.8)	2.2 (0.7-9.0)	1.1 (0.4-4.4)
Spirits	Percent consuming spirits	81%	79%	79%	77%
	Median (IR)	8.0 (1.8-21.3)	10.7 (3.7-22.9)	10.7 (3.7-22.9)	10.7 (2.7-11.4)

^a The interquartile range (IR) is the distance between the 25th and 75th percentiles for the distribution under consideration.

^b Total alcohol contains not only beer, wine, and spirits but also fortified wine and other miscellaneous drinks such as grapefruit and gin.

drinking some alcohol. Beer and spirit use was much more common than wine drinking.

The diet in this population was characterized by a high daily intake of fiber (median, 24 g), fat (median 117 g, or 39 percent of calories), and calcium (median, 1.3 g). On average, drinkers had a higher intake of total energy while consuming less coffee, starch, sweets and sugar, and calcium than nondrinkers (Table 2). Intake of ethanol was correlated significantly with age (Spearman's correlation coefficient, $r_s = -0.17$), level of smoking ($r_s = 0.19$), total energy ($r_s = 0.11$), coffee ($r_s = -0.18$), sweets and sugar ($r_s = -0.18$), and starch ($r_s = -0.16$).

To evaluate the association between alcohol consumption and colorectal cancer incidence, we first examined the effects of drinking status (1, 0 variable, D, for any *cf* none) and amount consumed (defined by quartile of ethanol) through a Cox regression model that included age at randomization. This simple model produced seemingly contradictory results. The RR for drinking ($RR_D = 0.6$, $CI = 0.3-1.1$) implied that drinkers were possibly at lower risk of colorectal cancer compared with nondrinkers, whereas an increasing trend for amount consumed ($RR_{Q2} = 1.1$ [$CI = 0.6-1.9$], $RR_{Q3} = 1.4$ [$CI = 0.9-2.4$], $RR_{Q4} = 1.7$ [$CI = 1.0-2.9$]) suggested that greater consumption was associated directly with increasing risk.

Because of this apparent paradox, we examined the validity of the Cox model PH assumption. We first divided the follow-up period into four time intervals: < 2 years, ≥ 2 years to < 4 years, ≥ 4 years to < 6 years, and ≥ 6 years. The number of colorectal cancer cases, person-years at risk, crude incidence rate for drinkers and nondrinkers, and age-adjusted incidence rate ratio estimated from a Cox regression model are shown in Table 3 for each follow-up period. The latter model relaxed the PH assumption by allowing the effect of drinking status to differ across the four follow-up periods. The incidence

rate ratio of drinkers *cf* nondrinkers increased from 0.39 during the first two years of follow-up to 2.24 for the period after six years (three degrees of freedom (d.f.) chi-square statistic for testing the equality of these four rate ratios = 6.5, $P = 0.09$). Figure 1 depicts the variation of incidence rate ratios with follow-up time, and shows that the estimated incidence rate ratio varies in a regular manner over the entire follow-up period. This interaction was tested statistically by adding to the simple Cox regression model a 'linear time \times D' term, which was significant ($P = 0.002$).

We also examined the PH assumption regarding the effect of quantity of alcohol consumed. In contrast to the time-varying risk of drinking *cf* not drinking shown in Table 3 and Figure 1, the risk of colorectal cancer associated with increasing alcohol consumption among drinkers did not change significantly during follow-up ($P = 0.39$). Beverage-specific risk associated with drinking any beer, wine, or spirits (*cf* nondrinkers) also increased over follow-up time, and relationships similar to those for colorectal cancer were observed for colon and rectal cancer risk separately (data not shown). We also compared an age-adjusted model with three indicator variables representing quartiles of ethanol consumption based on the distribution of alcohol in the whole cohort (drinkers and nondrinkers) that either included or excluded the first three years of follow-up. When the full period of follow-up was considered, we obtained RRs of 0.9 ($CI = 0.5-1.4$), 1.2 ($CI = 0.7-1.9$), and 1.3 ($CI = 0.8-2.1$) comparing second, third, and fourth quartiles with the first quartile (which included light-drinkers and nondrinkers), whereas exclusion of the first three years of follow-up resulted in RR estimates of 1.5 ($CI = 0.8-3.0$), 1.7 ($CI = 0.9-3.4$), and 1.8 ($CI = 0.9-3.5$). The analyses which follow were based on Cox models including variables for drinking status (D), amount consumed, age, and the (linear time \times D) interaction.

Table 2. Medians and interquartile ranges^a (IR) for dietary and other factors by level of alcohol consumption, Finnish men

Factor	Alcohol consumption quartiles ^b (ethanol g/day)			
	≤ 2.6	$> 2.6 - \leq 11.0$	$> 11.0 - \leq 25.6$	> 25.6
Total energy (kcal/day)	2,667 (2,190-3,202)	2,636 (2,200-3,160)	2,714 (2,264-3,240)	2,868 (2,394-3,442)
Fat (g/day)	118 (94-147)	116 (94-145)	118 (95-146)	116 (92-146)
Protein (g/day)	99 (83-119)	99 (83-119)	101 (83-121)	100 (82-121)
Fiber (g/day)	26 (20-33)	25 (19-32)	24 (18-31)	22 (17-30)
Starch (g/day)	150 (120-188)	143 (114-179)	139 (109-174)	129 (98-165)
Sweets and sugar (g/day)	40 (24-58)	35 (21-52)	32 (19-48)	28 (16-44)
Coffee (g/day)	660 (440-880)	600 (440-770)	550 (350-770)	450 (300-660)
Calcium (mg/day)	1,379 (1,054-1,743)	1,336 (1,008-1,688)	1,334 (1,006-1,710)	1,297 (953-1,691)
Body mass index (kg/m ²)	25.7 (23.4-28.2)	25.9 (23.8-28.4)	26.0 (23.7-28.6)	26.2 (23.9-28.8)
Number of cigarettes/day	20 (13-24)	20 (15-25)	20 (15-25)	20 (20-30)

^a The interquartile range (IR) is the distance between the 25th and 75th percentiles for the distribution under consideration.

^b Cutoffs are based on the distribution of alcohol among the whole cohort: drinkers and nondrinkers).

Table 3. Effect of follow-up time on the association between drinking status and colorectal cancer, Finnish men

Follow-up time (yrs)	Drinkers			Nondrinkers			Drinkers:nondrinkers
	Number of cases	Person-years at risk	Incidence rate $\times 10^3$ (CI) ^a	Number of cases	Person-years at risk	Incidence rate $\times 10^3$ (CI) ^a	Age-adjusted incidence rate ratio ^b (CI)
< 2	25	47,517	0.5 (0.4-0.6)	9	5,959	1.5 (1.1-2.0)	0.4 (0.2-0.8)
≥ 2 < 4	39	45,890	0.8 (0.7-1.0)	8	5,704	1.4 (1.0-1.9)	0.7 (0.3-1.5)
≥ 4 < 6	38	39,388	1.0 (0.8-1.1)	3	4,779	0.6 (0.3-1.0)	1.7 (0.5-5.6)
≥ 6 < 8	17	13,832	1.2 (1.0-1.5)	1	1,624	0.6 (0.2-1.4)	2.2 (0.3-16.8)

^a CI = 95% confidence interval; arc sin transformation for CI on rates, $y = 2\sin^{-1}(\sqrt{x})$.

^b Age-adjusted by Cox regression using four age groups: 50-54, 55-59, 60-64, 65-69. Test for trend using Cox regression P -value = 0.02.

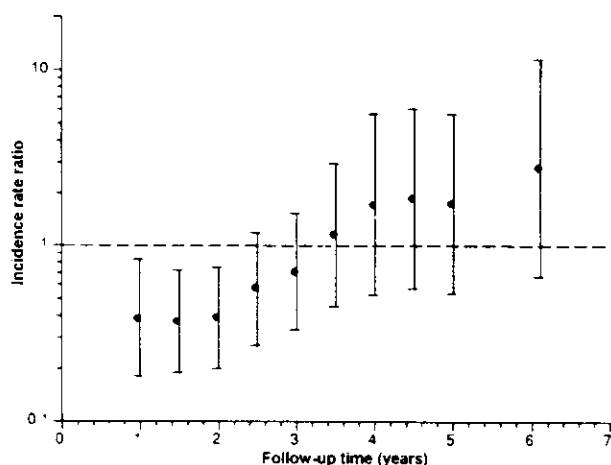


Figure 1. Incidence rate ratio (drinkers *cf* nondrinkers) over follow-up time. The simple Cox model was applied to a series of different follow-up periods, 0-24 months, 7-30 months, ... 55-92 months, to construct this figure. Overlapping periods resulted in a sufficient number of cases (~ 40) within each follow-up period.

The association between alcohol and colorectal cancer differed significantly depending on whether subjects did or did not receive β -carotene supplementation (two d.f. model chi-square = 7.65, $P = 0.02$), but was not related to vitamin E treatment (two d.f. model chi-square = 4.053, $P = 0.13$). Because of the small number of cases who did not drink ($n = 21$) and the non-proportional hazards over time for drinkers compared with nondrinkers, we could not reliably estimate risk stratified by both drinking status and follow-up time for the β -carotene and non- β -carotene groups separately, as exemplified by the wide CIs obtained when the first three years of follow-up were excluded (RR = 5.5, CI = 0.8-39.8, for the β -carotene group; RR = 1.4, CI = 0.4-4.6, for the non- β -carotene group). We therefore focused on the effect

of alcohol on colorectal cancer among alcohol consumers only (i.e., 89 percent of the study population).

Tables 4 and 5 show RRs for colorectal cancer by quartile of ethanol and beverage consumption among drinkers according to β -carotene treatment group. Because the RR estimates from age-adjusted and fully-adjusted models did not differ, we present only those results from multivariable models that included age, job-related physical activity, and intakes of total energy, sweets and sugar, coffee, calcium, and starch. The effect of alcohol on colorectal cancer risk did not differ by levels of each of these variables or by number of cigarettes smoked per day.

Among subjects who did not receive β -carotene, colorectal cancer risk increased with total ethanol consumption (Table 4). We observed an RR of 2.7 for the highest compared with the lowest quartile ($P = 0.02$), and the test for trend was also statistically significant ($P = 0.01$). In terms of ethanol consumption in g/day, an RR of 1.01 (CI = 1.00-1.02, $P = 0.01$) was obtained and is equivalent to a 17 percent increase in risk for each drink consumed, assuming each drink contains on average 13 grams of ethanol.¹⁹ These findings were driven primarily by a strong association between colon cancer and amount of alcohol (P trend = 0.01) in the non- β -carotene group, while rectal cancer risk was elevated to lesser degree. Table 5 shows that both beer and spirits contributed to the positive association between alcohol consumed and colorectal cancer (P trend = 0.05 for both beer and spirits). The RRs by level of beer drinking suggested a 70 percent risk increase for colorectal cancer among drinkers in the highest quartile (median for quartile, 22 g/day) compared with drinkers in the lowest quartile (median, 0.9 g/day); whereas for spirits, the highest quartile (median, 23 g/d) demonstrated a 2.5-fold risk increase compared with the lowest quartile (median, 0.9 g/d) ($P = 0.04$). The association between colorectal cancer

Table 4. Adjusted relative risks (RR) and 95% confidence intervals (CI) of colorectal cancer, colon cancer, and rectal cancer by level of total ethanol use among drinkers according to β -carotene treatment. Finnish men

Quartiles (ethanol g/day)		No β -carotene			β -carotene		
		No.	RR ^a	(CI)	No.	RR ^a	(CI)
Colorectal cases	Q1 ^b : ≤ 5.3	8	1.0	—	17	1.0	—
	Q2: $> 5.3 \leq 13.4$	10	1.3	(0.5-3.4)	16	0.9	(0.5-1.9)
	Q3: $> 13.4 \leq 27.7$	15	2.0	(0.8-4.8)	17	1.1	(0.5-2.1)
	Q4: > 27.7	20	2.7	(1.2-6.4)	16	1.0	(0.5-2.1)
	P trend		0.01			0.79	
Colon cases	Q1: ≤ 5.3	5	1.0	—	9	1.0	—
	Q2: $> 5.3 \leq 13.4$	7	1.5	(0.5-4.8)	9	1.0	(0.4-2.6)
	Q3: $> 13.4 \leq 27.7$	8	1.8	(0.6-5.6)	11	1.4	(0.6-3.4)
	Q4: > 27.7	15	3.6	(1.3-10.4)	12	1.6	(0.6-4.1)
	P trend		0.01			0.24	
Rectal cases	Q1: ≤ 5.3	3	1.0	—	8	1.0	—
	Q2: $> 5.3 \leq 13.4$	3	1.0	(0.2-5.1)	7	0.8	(0.3-2.3)
	Q3: $> 13.4 \leq 27.7$	7	2.3	(0.6-9.0)	6	0.7	(0.2-2.2)
	Q4: > 27.7	5	1.5	(0.3-6.7)	4	0.5	(0.1-1.6)
	P trend		0.37			0.25	

^a These RRs are adjusted for age, physical activity during work, and intakes of total energy, starch, sweet and sugar, coffee, and calcium.

^b Cutoffs for quartiles are based on the distribution of alcohol among drinkers only.

Table 5. Adjusted relative risks (RR) and 95% confidence intervals (CI) of colorectal cancer by level of consumption^a of alcohol subtypes among drinkers according to β -carotene treatment. Finnish men

Quartiles (ethanol g/d)		No β -carotene			β -carotene		
		No.	RR ^b	(CI)	No.	RR ^b	(CI)
Beer	Q1: ≤ 1.7	8	1.0	—	17	1.0	—
	Q2: $> 1.7 \leq 4.6$	3	0.3	(0.1-1.3)	6	0.4	(0.2-1.0)
	Q3: $> 4.6 \leq 11.6$	13	1.5	(0.6-4.0)	21	1.2	(0.6-2.4)
	Q4: > 11.6	16	1.7	(0.7-4.1)	11	0.7	(0.3-1.5)
	P trend		0.05			0.94	
Wine	Q1: ≤ 0.7	3	1.0	—	4	1.0	—
	Q2: $> 0.7 \leq 2.1$	6	1.3	(0.3-5.2)	6	1.1	(0.3-3.9)
	Q3: $> 2.1 \leq 4.6$	3	0.6	(0.1-3.2)	6	1.3	(0.2-7.0)
	Q4: > 4.6	2	0.4	(0.1-2.4)	8	1.7	(0.2-15.6)
	P trend		0.18			0.33	
Spirits	Q1: ≤ 1.8	8	1.0	—	16	1.0	—
	Q2: $> 1.8 \leq 8.0$	14	1.8	(0.7-4.3)	15	1.0	(0.4-2.2)
	Q3: $> 8.0 \leq 21.3$	10	1.6	(0.6-4.0)	12	1.0	(0.4-2.4)
	Q4: > 21.3	19	2.5	(1.0-6.1)	16	1.1	(0.5-2.4)
	P trend		0.05			0.75	

^a A glass of beer, wine, or spirits contains on average 13, 11, and 15 grams of ethanol respectively.¹⁹

^b These beverage-specific RRs are adjusted simultaneously for other beverages as well as for age, physical activity during work, and intakes of total energy, starch, sweet and sugar, coffee, and calcium.

and wine consumption in the non- β -carotene group was not significant but tended to be negative (Table 5).

In contrast to the non- β -carotene group, the amount of alcohol among drinkers was not associated significantly with risk of colorectal cancer (colon or rectum) in the β -carotene supplemented group (Table 4). The total ethanol and beverage-specific RRs, with the exception of

wine drinking, were closer to the null than for the non- β -carotene group (Table 5).

Discussion

In the present study, male smokers who drank had increased risk of colorectal cancer, especially colon cancer,

as they consumed more alcohol. This finding was not affected by adjustment for potential confounding factors including several dietary variables, smoking, study area, education, and BMI. Several observational studies²⁰⁻²⁶ report higher colon cancer risk among drinkers of any alcohol or specific alcoholic beverages, while others²⁷⁻³² do not support a positive association in males (for review, see Kune *et al*⁹). Although the reported risk estimates vary depending on the alcohol categories and the reference group chosen, in at least three studies,^{20,26,33} risk increased among males up to two- to 2.5-fold as they consumed more alcohol. Several studies^{20,23-25,27,29,30,34-36} also demonstrate positive associations between alcohol and rectal cancer. In our study, none of the findings for rectal cancer among drinkers were significant although the directionality of the estimates suggested that risk of rectal cancer may be increased with higher levels of alcohol consumption. The lack of a significant dose-response effect among drinkers and the wide CIs observed, however, warrant cautious interpretation of these findings.

In our study, both beer and spirits tended to be associated positively with colorectal cancer among drinkers. While some studies have found a positive alcohol/colorectal-cancer association with only one type of beverage,^{23,26} others³⁵ have observed an increase in risk for all beverage types. The latter study along with ours suggest that ethanol, rather than another constituent present in a certain beverage, may be responsible for the association observed.

Of note in our study was the observation that the association between colorectal cancer and drinking any alcohol (but not the amount of alcohol) changed over time, with abstinence appearing harmful early in follow-up. Although possibly a chance finding, one explanation for this apparent change in risk over time is that preclinical disease (*i.e.*, undiagnosed colorectal cancer) was more prevalent at the start of the study among nondrinkers than among drinkers, and that these cases were diagnosed early in the study. This could occur if, for example, participants who reported abstinence from alcohol use over the preceding 12 months¹³ were comprised of both never-drinkers and ex-drinkers, and the ex-drinkers had stopped drinking because of poor health secondary to either occult bowel cancer or another illness. Indeed, our data substantiate prior alcohol use among some of our 'non-drinkers,' since three percent had one or more hospital admissions for alcohol-related diseases such as alcoholic cirrhosis (this percentage probably greatly underestimates the actual number of ex-drinkers misclassified as abstainers, particularly men with a history of moderate alcohol intake). Further, because ex-drinkers are more likely to be ill³⁷ and visit physicians more often, increased screening could result in the earlier diagnosis of colorectal cancer. The issue of potential bias intro-

duced by pre-existing disease was elaborated by Shaper and colleagues³⁸ in the context of the U-shaped relationship observed between total mortality and alcohol intake. In the interpretation of their findings, the authors did not believe moderate drinking was protective; rather, that nondrinkers were not an appropriate reference group. Indeed, after evaluating changes in drinking behavior over time among men aged 40 to 59 years who were part of the British Regional Heart Study, Wannamethee and colleagues³⁷ concluded that as many as 70 percent of the nondrinking population at follow-up was made up of ex-drinkers. Heavy and moderate drinkers were more likely to reduce or stop alcohol consumption than light drinkers, and often because of ill health.³⁷ Our finding that exclusion of the early follow-up period (*i.e.*, less than three years) strengthened the positive association between drinking and colorectal cancer also suggests that preclinical disease may have been a factor in our study.

Interestingly, the positive association between level of alcohol consumption and colorectal cancer risk among drinkers was attenuated in subjects supplemented with β -carotene. The results were of marginal statistical significance, however, and may be secondary to chance. This, coupled with the lack of consistency across beverage types, warrants their cautious interpretation. Further, we were unable to assess adequately any effect modification by β -carotene of the drinking-status/colorectal-cancer association because of the non-proportionality of the drinking/nondrinking risk over time and small number of nondrinking cases. Although RR estimates that excluded the first three years of follow-up suggest a positive interaction, with β -carotene increasing the risk due to drinking, information from other studies, including β -carotene intervention trials, is needed to evaluate more clearly the possible effects of β -carotene on alcohol-associated tumors.

One of the important strengths of this investigation is that assessment of exposures took place at baseline on individuals without known cancer, thereby avoiding both recall bias and any effects of cancer treatment on them. Our detailed dietary instrument¹³ permitted assessment of not only total ethanol consumption but specific beverage type, quantity, and frequency. The questionnaire data also afforded adjustment for a large number of dietary factors relevant to cancer of the large bowel. Our study also had limitations. The parent investigation, and hence the present analysis, was limited to older male smokers; the relevance to other subpopulations can only be speculated. For example, while adjustment for number of cigarettes smoked daily did not alter the findings, we do not know if the associations are different in nonsmokers. Moreover, in addition to the issue of appropriate classification of ex-drinkers raised above, some drinkers could have underreported their current drinking habits, lead-

ing to misclassification. We do not know whether misclassification of current alcohol consumption occurred in our data, or whether it differed by case status. Comparison with 1985 Finnish State Alcohol Company (ALKO) statistics shows that annual total alcohol consumption (100 percent alcohol) averaged 23 g/day for the population aged 18 years or older,³⁹ a figure somewhat higher than the average intake in this study (18 g/day), but younger individuals (<50 years old) tend to drink more. Finally, some factors that potentially could affect colorectal cancer risk, such as a history of adenomatous polyps or family history of colorectal cancer, were not available for adjustment.

Apart from methodologic differences, other factors may explain the divergence in results obtained in epidemiologic studies that have investigated the role of alcohol in colorectal cancer. The effect of alcohol on colorectal cancer might depend on the drinking pattern of the population under study. In Finland, drinking has been reported to be rare during the work week, and occurs mostly at social events – rather than during meals *per se* – with large quantities being consumed.³⁹ Such a 'binge' pattern of drinking may well have different effects on rectal or colon cells compared with a more regular pattern of drinking (i.e., smaller quantities but on a daily basis).

Several mechanisms by which alcohol might promote carcinogenesis have been proposed.^{9,41} Alcohol could activate procarcinogens by inducing changes in cytochrome P-450 in the liver,⁴¹ or promote carcinogenesis by delaying DNA repair or by interfering with DNA methylation.^{42,43} Individuals who drink alcohol may have decreased intake or bioavailability of specific nutrients that may prevent cancer.⁴⁴ For example, chronic or acute alcohol use is associated with folate deficiency⁴⁵ and it is possible that the combination of low folate status and high alcohol consumption could result in lower S-adenosylmethionine levels and subsequent DNA hypomethylation.⁴⁶ Giovannucci and others²¹ have shown that high alcohol intake combined with low methionine and folate intake increases colon cancer risk. In addition to the above, acetaldehyde found in the large intestine⁴⁷ may contribute to large bowel carcinogenesis.⁴¹ Ethanol is oxidized to acetaldehyde via alcohol dehydrogenase in the liver and stomach,⁴⁸ and by bacteria in the colon.⁴⁹ Further, chronic ethanol consumption causes induction of the microsomal ethanol oxidizing system (MEOS) that can transform alcohol to acetaldehyde, activate (or deactivate) xenobiotics and liberate free radicals.⁴⁸ Lieber⁴⁸ has noted that acetaldehyde may lead to decreased glutathione levels. A decrease in this free radical scavenger, coupled with an increased production of free radicals (by-products of the MEOS) in colonic cells could lead to toxic reactions eventually resulting in cancer promo-

tion. Hypothetically, β -carotene supplementation and elevated concentrations of β -carotene in colonic mucosa,⁵⁰ might counteract the effect of ethanol by quenching free radicals such as peroxy radicals.⁵¹ This mechanism could explain, in theory, the results we obtained among spirit and beer drinkers. Vitamin E, another known antioxidant, did not interact significantly with alcohol in our study. It is worth noting, however, that the direction of the vitamin E effect among drinkers was similar to the one observed for β -carotene (data not shown).

In summary, this study showed that in male smokers who drink alcohol, ingesting greater amounts of alcohol increases risk of colorectal cancer, especially colon cancer. We further observed that drinkers are at greater risk compared with nondrinkers, but only after about three-and-a-half years of study follow-up. While these findings support the hypothesis that alcohol plays a role in the etiology of colon cancer, further investigation of the relationship is warranted. Lifetime alcohol consumption may be more relevant to pathogenesis than current intake alone and should be assessed. Our results also suggest that similar prospective investigations should give greater consideration to the possible effects of preclinical disease and stratify their analyses based on time to diagnosis.

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